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(54) Title: ARYLSULFONAMIDO-SUBSTITUTED HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE INHIBITORS			
(57) Abstract Compounds of formula (I) wherein R, R ₁ , R ₂ and Ar are as defined in the specification, have valuable pharmaceutical properties and are effective especially as matrix metalloproteinase inhibitors, for example for the treatment of arthritis. They are prepared in a manner known per se.			
<div style="display: flex; align-items: center; justify-content: center;"> $\begin{array}{c} \text{HO}-\text{N}-\text{C} \begin{array}{l} \text{O} \\ \parallel \end{array} \text{C} \begin{array}{l} \text{R}_1 \\ \end{array} \text{CH}_2 \begin{array}{l} \text{O} \\ \parallel \end{array} \text{S}-\text{Ar} \\ \begin{array}{l} \\ \text{H} \end{array} \quad \begin{array}{l} \\ \text{R}_2 \end{array} \quad \begin{array}{l} \text{O} \\ \parallel \end{array} \end{array} \quad (I)$ </div>			

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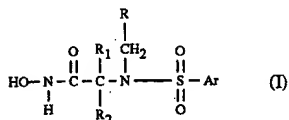
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ARYLSULFONAMIDO-SUBSTITUTED HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE INHIBITORS.

The present invention relates to the compounds of formula I



wherein

Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkyl)piperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is C₈-C₁₀-cycloalkyl, (N-acyl-piperidyl)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy)-lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl), N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-cycloalkyl, (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl, (amino, mono- or di-lower alkylamino or acylamino)-C₅-C₁₀-cycloalkyl, 2-oxo-(pyrrolidinyl, piperidyl or hexahydroazepinyl);

R₂ is hydrogen or lower alkyl;

pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof;

further to a process for the preparation of these compounds, to pharmaceutical compositions comprising these compounds, to the use of these compounds for the therapeutic treatment of the human or animal body or for the manufacture of a pharmaceutical composition.

Preferred are said compounds of formula I, wherein Ar is monocyclic carbocyclic aryl such as phenyl or phenyl mono-, di- or tri-substituted by C₁-C₁₀-alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, C₃-C₇-cycloalkyl-lower alkoxy, (lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl or C₃-C₇-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino or mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is heterocyclic monocyclic aryl such as thienyl or thienyl substituted by lower alkyl; the other symbols have meaning as defined; pharmaceutically acceptable prodrug derivatives thereof; and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula I

wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₁₀-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; or Ar is phenyl substituted by C₃-C₇-cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C₃-C₇-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono-

or di-lower alkylamino or, on adjacent carbon atoms, by C_1 - C_2 -alkylenedioxy or oxy- C_2 - C_3 -alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolynyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; biphenyl-lower alkyl wherein biphenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; (pyridyl, thienyl, quinolynyl or thiazolyl)-lower alkyl, trifluoromethyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl-lower alkyl, (oxa or thia)- C_3 - C_6 -cycloalkyl, [(oxa or thia)- C_3 - C_6 -cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R_1 is pyrrolidinyl; hexahydroazepinyl; N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl); N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C_5 - C_{10} -oxacycloalkyl; C_5 - C_{10} -thiacycloalkyl; (hydroxy or oxo)- C_5 - C_{10} -cycloalkyl; (hydroxy or oxo)- C_5 - C_{10} -thiacycloalkyl; (hydroxy or oxo)- C_5 - C_{10} -oxacycloalkyl; or (amino, mono- or dialkylamino or lower alkanoylamino)- C_5 - C_{10} -cycloalkyl;

R_2 is hydrogen or lower alkyl;

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Especially preferred are the compounds of formula I

wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1 - C_7 -alkoxy, hydroxy, phenyl-lower alkoxy, C_3 - C_7 -cycloalkyl-lower alkoxy, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1 - C_2 -alkylenedioxy or oxy- C_2 - C_3 -alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen; lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-,

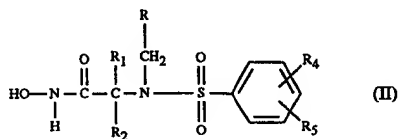
di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenyl; biphenyl-lower alkyl; (pyridyl or thienyl)-lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl; hydroxy-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is pyrrolidinyl; hexahydroazepinyl; N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl); N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-cycloalkyl; (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl; or (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A particular embodiment of the invention relates to the compounds of formula II



wherein

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino,

mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

R₁ is pyrrolidinyl, hexahydroazepinyl, N-lower alkyl-(pyrrolidinyl or hexahydroazepinyl), C₅-C₇-oxacycloalkyl, C₅-C₇-thiacycloalkyl, (hydroxy or oxo)-cyclohexyl, (amino, mono- or di-lower alkylamino)-cyclohexyl or 2-oxo-hexahydroazepinyl;

R₂ is hydrogen;

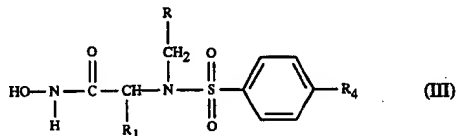
R₄ is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

R₅ is hydrogen, lower alkyl or halogen;

or R₄ and R₅ together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy, oxyethylene or oxypropylene;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Particularly preferred are the compounds of formula III



wherein R represents lower alkyl, trifluoromethyl, C₅-C₇-cycloalkyl, (oxa or thia)-C₄-C₅-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R₁ represents C₅-C₇-oxacycloalkyl or (hydroxy, oxo or di-lower alkylamino)-cyclohexyl; R₄ represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a

pharmaceutically acceptable salt thereof.

Further preferred are compounds of formula III wherein R represents monocyclic carbocyclic aryl or monocyclic heterocyclic aryl; R₁ and R₄ have meaning as defined above; pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof.

More particularly preferred are said compounds of formula III wherein R represents heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R₁ represents 2- or 3-tetrahydrofuranyl; and R₄ represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

A further preferred embodiment relates to said compounds of formula III wherein R represents 2-, 3- or 4-pyridyl or phenyl; R₁ represents 2- or 3-tetrahydrofuranyl; and R₄ represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Particularly preferred are said compounds of formula III wherein R represents 3-pyridyl or 4-pyridyl; R₁ represents 2-tetrahydrofuranyl; and R₄ represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

As sub-groups of any group of compounds of formula I mentioned herein are emphasized:

(a) the compounds of formula I wherein R₁ is C₈-C₁₀-cycloalkyl, (N-lower alkoxycarbonyl-piperidyl)-(lower alkoxy)-lower alkyl, pyrrolidinyl, N-(lower alkoxycarbonyl or di-lower alkylamino-lower alkanoyl)-(piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, hydroxy-C₅-C₁₀-cycloalkyl, (hydroxy)-C₅-C₁₀-oxacycloalkyl, (di-lower alkylamino, di-lower alkylamino-lower alkanoylamino or lower alkoxy-carbonylamino)-C₅-C₁₀-cycloalkyl or 2-oxo-piperidyl; (b) the compounds of formula I wherein R₁ is C₈-C₁₀-cycloalkyl, (N-lower alkoxycarbonyl-piperidyl)-(lower alkoxy)-lower alkyl, pyrrolidinyl, N-(lower alkoxycarbonyl or di-lower alkylamino-lower alkanoyl)-(piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, hydroxy-C₅-C₁₀-cycloalkyl, (hydroxy)-C₅-C₁₀-oxacycloalkyl, (di-lower alkylamino or di-lower alkylamino-lower

alkanoylamino)-C₅-C₁₀-cycloalkyl or 2-oxo-piperidyl; (c) the compounds of formula I wherein R is lower alkyl, 2-, 3- or 4-pyridyl or phenyl; (d) the compounds of formula I wherein R is 2-, 3- or 4-pyridyl or phenyl; (e) the compounds of formula I wherein Ar is lower alkoxy-phenyl.

The invention relates especially to the specific compounds described in the examples, pharmaceutically acceptable prodrug derivatives thereof and pharmaceutically acceptable salts thereof, and in particular to the specific compounds described in the examples and pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable prodrug derivatives are those that may be convertible by solvolysis or under physiological conditions to the free hydroxamic acids of the invention and represent such hydroxamic acids in which the CONHOH group is derivatized in form of an O-acyl or an optionally substituted O-benzyl derivative. Preferred are the optionally substituted O-benzyl derivatives.

The compounds of the invention depending on the nature of the substituents, possess one or more asymmetric carbon atoms. The resulting diastereoisomers and enantiomers are encompassed by the instant invention.

Preferred are the compounds of the invention wherein the asymmetric carbon in the above formulae (to which are attached R₁ and/or R₂) corresponds to that of a D-aminoacid precursor and is assigned the (R)-configuration.

The general definitions used herein have the following meaning within the scope of the present invention, unless otherwise specified.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms, and represents for example methyl, ethyl, propyl, butyl, isopropyl or isobutyl.

A lower alkoxy (or alkyloxy) group preferably contains 1-4 carbon atoms, advantageously

1-3 carbon atoms, and represents for example ethoxy, propoxy, isopropoxy, or most advantageously methoxy.

Halogen (halo) preferably represents chloro or fluoro but may also be bromo or iodo.

Mono- or poly-halo-lower alkyl represents lower alkyl preferably substituted by one, two or three halogens, preferably fluoro or chloro, e.g. trifluoromethyl or trifluoroethyl.

Aryl represents carbocyclic or heterocyclic aryl.

Prodrug acyl derivatives are preferably those derived from an organic carbonic acid, an organic carboxylic acid or a carbamic acid.

An acyl derivative which is derived from an organic carboxylic acid is, for example, lower alkanoyl, phenyl-lower alkanoyl or unsubstituted or substituted aroyl, such as benzoyl.

An acyl derivative which is derived from an organic carbonic acid is, for example, alkoxycarbonyl, especially lower alkoxycarbonyl, which is unsubstituted or substituted by carbocyclic or heterocyclic aryl or is cycloalkoxycarbonyl, especially C_3-C_7 -cycloalkyloxycarbonyl, which is unsubstituted or substituted by lower alkyl.

An acyl derivative which is derived from a carbamic acid is, for example, amino-carbonyl which is substituted by lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, carbocyclic or heterocyclic aryl, lower alkylene or lower alkylene interrupted by O or S.

Prodrug optionally substituted O-benzyl derivatives are preferably benzyl or benzyl mono-, di-, or tri-substituted by e.g. lower alkyl, lower alkoxy, amino, nitro, halogen and/or trifluoromethyl.

Carbocyclic aryl represents monocyclic or bicyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, hydroxy, halogen, cyano, trifluoromethyl, lower alkylenedioxy and oxy- C_2-C_3 -alkylene; or 1- or 2-naphthyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy- C_2-C_3 -alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy- C_2-C_3 -alkylene-phenyl

is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is phenyl or phenyl monosubstituted by lower alkoxy, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl monosubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by e.g. lower alkyl or halogen. Pyridyl represents 2-, 3- or 4-pyridyl, advantageously 2- or 3-pyridyl. Thienyl represents 2- or 3-thienyl, advantageously 2-thienyl. Quinolinyl represents preferably 2-, 3- or 4-quinolinyl, advantageously 2-quinolinyl. Isoquinolinyl represents preferably 1-, 3- or 4-isoquinolinyl. Benzopyranyl, benzothiopyranyl represent preferably 3-benzopyranyl or 3-benzothiopyranyl, respectively. Thiazolyl represents preferably 2- or 4-thiazolyl, advantageously 4-thiazolyl. Triazolyl is preferably 1-, 2- or 5-(1,2,4-triazolyl). Tetrazolyl is preferably 5-tetrazolyl. Imidazolyl is preferably 4-imidazolyl.

Preferably, heterocyclic aryl is pyridyl, quinolinyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted, by lower alkyl or halogen; and in particular pyridyl.

Biaryl is preferably carbocyclic biaryl, e.g. biphenyl, namely 2, 3 or 4-biphenyl, advantageously 4-biphenyl, each optionally substituted by e.g. lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano.

C₃-C₁₀-Cycloalkyl, e.g. C₈-C₁₀-cycloalkyl, represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 (or 8, respectively) to 10 ring carbons and is advantageously cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl optionally substituted by lower alkyl.

(Oxa or thia)-C₃-C₆-cycloalkyl represents a saturated cyclic radical wherein 1 or 2, preferably 1, oxygen or sulfur atom(s) and preferably 4-5 carbon atoms form a ring, e.g. tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl or tetrahydrothienyl. (Oxa or thia)-C₇-C₁₀-cycloalkyl is defined analogously, and represents e.g. oxacycloheptyl or

oxacyclooctyl.

Oxa-cyclohexane means tetrahydropyran, and thia-cyclohexane means tetrahydrothiopyran. C₅-(Oxa or thia)cycloalkyl means tetrahydrofuranyl or tetrahydrothienyl, respectively [each containing 4 ring carbon atoms and 1 ring hetero atom (oxygen or sulfur, respectively)].

Oxo represents the substituent =O; for example, 4-oxocyclohexyl is identical with "cyclohexanone-4-yl".

Carbocyclic aryl-lower alkyl represents preferably straight chain or branched aryl-C₁-C₄-alkyl in which carbocyclic aryl has meaning as defined above, e.g. benzyl or phenyl-(ethyl, propyl or butyl), each unsubstituted or substituted on phenyl ring as defined under carbocyclic aryl above, advantageously optionally substituted benzyl.

Heterocyclic aryl-lower alkyl represents preferably straight chain or branched heterocyclic aryl-C₁-C₄-alkyl in which heterocyclic aryl has meaning as defined above, e.g. 2-, 3- or 4-pyridylmethyl or (2-, 3- or 4-pyridyl)-(ethyl, propyl or butyl); or 2- or 3-thienylmethyl or (2- or 3-thienyl)-(ethyl, propyl or butyl); 2-, 3- or 4-quinolylmethyl or (2-, 3- or 4-quinolyl)-(ethyl, propyl or butyl); or 2- or 4-thiazolylmethyl or (2- or 4-thiazolyl)-(ethyl, propyl or butyl).

Cycloalkyl-lower alkyl represents e.g. (cyclopentyl- or cyclohexyl)-(methyl or ethyl).

Biaryl-lower alkyl represents e.g. 4-biphenyl-(methyl or ethyl).

Acyl is derived from an organic carboxylic acid, carbonic acid or carbamic acid.

Acyl represents e.g. lower alkanoyl, carbocyclic aryl-lower alkanoyl, lower alkoxycarbonyl, aroyl, di-lower alkylaminocarbonyl or di-lower alkylamino-lower alkanoyl. Preferably, acyl is lower alkanoyl.

Acylamino represents e.g. lower alkanoylamino or lower alkoxycarbonylamino.

Acylamino-lower alkyl in R is R₃-CONH-lower alkyl in which R₃ represents e.g. lower alkyl, lower alkoxy, aryl-lower alkyl, aryl-lower alkoxy, carbocyclic or heterocyclic aryl,

di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, N-alkylpiperidyl, or (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, pyridyl or N-lower alkylpiperidyl)-lower alkyl.

Lower alkanoyl represents e.g. C₁-C₇-alkanoyl including formyl, and is preferably C₂-C₄-alkanoyl such as acetyl or propionyl.

Aroyl represents e.g. benzoyl or benzoyl mono- or di-substituted by one or two radicals selected from lower alkyl, lower alkoxy, halogen, cyano and trifluoromethyl; or 1- or 2-naphthoyl; and also e.g. pyridylcarbonyl.

Lower alkoxy carbonyl represents preferably C₁-C₄-alkoxy carbonyl, e.g. ethoxycarbonyl.

Lower alkylene represents either straight chain or branched alkylene of 1 to 7 carbon atoms and represents preferably straight chain alkylene of 1 to 4 carbon atoms, e.g. a methylene, ethylene, propylene or butylene chain, or said methylene, ethylene, propylene or butylene chain mono-substituted by C₁-C₃-alkyl (advantageously methyl) or disubstituted on the same or different carbon atoms by C₁-C₃-alkyl (advantageously methyl), the total number of carbon atoms being up to and including 7.

Esterified carboxyl is for example lower alkoxy carbonyl or benzyloxy carbonyl.

Amidated carboxyl is for example aminocarbonyl, mono- or di-lower alkylaminocarbonyl.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The compounds of the invention exhibit valuable pharmacological properties in mammals

including man and are particularly useful as inhibitors of matrix-degrading metalloproteinase enzymes (= metalloproteinases).

Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Pager's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (as reported in J. Leuk. Biol. 52 (2): 244-248, 1992).

As the compounds of the invention are inhibitors of stromelysin, gelatinase and/or collagenase and inhibit matrix degradation, they are particularly useful in mammals as agents for the treatment of e.g. osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, tumor metastasis, progression of HIV-infection and HIV-infection related disorders and osteoporosis.

Illustrative of the matrix degrading metalloproteinase inhibitory activity, compounds of the invention prevent the degradation of cartilage caused by exogenous or endogenous stromelysin in mammals. They inhibit e.g. the stromelysin-induced degradation of aggrecan (large aggregating proteoglycan), link protein or type IX collagen in mammals.

Beneficial effects are evaluated in pharmacological tests generally known in the art, and as illustrated herein.

The above-cited properties are demonstrable in in vitro and in vivo tests, using advantageously mammals, e.g. rats, guinea pigs, dogs, rabbits, or isolated organs and tissues, as well as mammalian enzyme preparations. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally or parenterally, advantageously orally, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-5} molar and 10^{-10} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 0.1 and 50 mg/kg.

One test to determine the inhibition of stromelysin activity is based on its hydrolysis of

Substance P using a modified procedure of Harrison et al (Harrison, R.A., Teahan J., and Stein R., A semicontinuous, high performance chromatography based assay for stromelysin, *Anal. Biochem.* **180**, 110-113 (1989)). In this assay, Substance P is hydrolyzed by recombinant human stromelysin to generate a fragment, Substance P 7-11, which can be quantitated by HPLC. In a typical assay, a 10 mM stock solution of a compound to be tested is diluted in the assay buffer to 50 μ M, mixed 1:1 with 8 μ g recombinant human stromelysin (mol. wt. 45-47 kDa, 2 Units; where 1 Unit produces 20 nmoles of Substance P 7-11 in 30 minutes) and incubated along with 0.5mM Substance P in a final volume of 0.125 ml for 30 minutes at 37°C. The reaction is stopped by adding 10 mM EDTA and Substance P 7-11 is quantified on RP-8 HPLC. The IC_{50} for inhibition of stromelysin activity and K_i are calculated from control reaction without the inhibitor. Typically, K_i values of from 10 to 200 nM are obtained.

Stromelysin activity can also be determined using human aggrecan as a substrate. This assay allows the confirmation *in-vitro* that a compound can inhibit the action of stromelysin on its highly negatively-charged natural substrate, aggrecan (large aggregating proteoglycan). Within the cartilage, proteoglycan exists as an aggregate bound to hyaluronate. Human proteoglycan aggregated to hyaluronate is used as an enzyme substrate. The assay is set up in 96-well microtiter plates allowing rapid evaluation of compounds. The assay has three major steps:

1) Plates are coated with hyaluronate (human umbilical chord, 400 μ g/ml), blocked with BSA (5 mg/ml), and then proteoglycan (human articular cartilage D1 - chondroitinase ABC digested, 2 mg/ml) is bound to the hyaluronate. Plates are washed between each step.

2) Buffers + inhibitor (1 to 5,000 nM) + recombinant human stromelysin (1-3 Units/well) are added to wells. The plates are sealed with tape and incubated overnight at 37°C. The plates are then washed.

3) A primary (3B3) antibody (mouse IgM, 1:10,000) is used to detect remaining fragments. A secondary antibody, peroxidase-linked anti-IgM, is bound to the primary antibody. OPD is then added as a substrate for the peroxidase and the reaction is stopped with sulfuric acid. The IC_{50} for inhibition of stromelysin activity is graphically derived and K_i is calculated. K_i values of about 50 nM or above are obtained.

Collagenase activity is determined as follows: ninety six-well, flat-bottom microtiter plates are first coated with bovine type I collagen (35 ug/well) over a two-day period at 30°C using a humidified and then dry atmosphere; plates are rinsed, air dried for 3-4 hours, sealed with Saran wrap and stored in a refrigerator. Human recombinant fibroblast collagenase and a test compound (or buffer) are added to wells (total volume = 0.1 ml) and plates are incubated for 2 hours at 35°C under humidified conditions; the amount of collagenase used per well is that causing approximately 80% of maximal digestion of collagen. The incubation media are removed from the wells, which are then rinsed with buffer, followed by water. Coomassie blue stain is added to the wells for 25 minutes, removed, and wells are again rinsed with water. Sodium dodecyl sulfate (20% in 50% dimethylformamide in water) is added to solubilize the remaining stained collagen and the optical density at 570 nm wave length is measured. The decrease in optical density due to collagenase (from that of collagen without enzyme) is compared to the decrease in optical density due to the enzyme in the presence of test compound, and percent inhibition of enzyme activity is calculated. IC_{50} 's are determined from a range of concentrations of inhibitors (4-5 concentrations, each tested in triplicate), and K_i values are calculated. K_i values of about 50 nM or above are obtained.

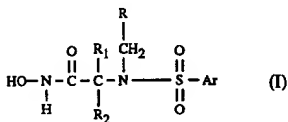
The effect of compounds of the invention in-vivo can be determined in rabbits. Typically, four rabbits are dosed orally with a compound up to four hours before being injected intra-articularly in both knees (N=8) with 40 Units of recombinant human stromelysin dissolved in 20 mM Tris, 10 mM $CaCl_2$, and 0.15 M NaCl at pH 7.5. Two hours later the rabbits are sacrificed, synovial lavage is collected, and keratan sulfate (KS) and sulfated glycosaminoglycan (S-GAG) fragments released into the joint are quantitated. Keratan sulfate is measured by an inhibition ELISA using the method of Thonar (Thonar, E.J.-M.A., Lenz, M.E., Klinsworth, G.K., Caterson, B., Pachman, L.M., Glickman, P., Katz, R., Huff, J., Keuttner, K.E. Quantitation of keratan sulfate in blood as a marker of cartilage catabolism, *Arthr. Rheum.* 28, 1367-1376 (1985)). Sulfated glycosaminoglycans are measured by first digesting the synovial lavage with streptomyces hyaluronidase and then measuring DMB dye binding using the method of Goldberg (Goldberg, R.L. and Kolibas, L. An improved method for determining proteoglycan synthesized by chondrocytes in culture. *Connect. Tiss. Res.* 24, 265-275 (1990)). For an i.v. study, a compound is solubilized in 1 ml of PEG-400, and for a p.o. study, a compound is administered in 5 ml of fortified corn starch per kilogram of body weight.

The effect in protecting against cartilage degradation in arthritic disorders is determined

e.g. in a surgical model of osteoarthritis described in Arthritis and Rheumatism, Vol. 26, 875-886 (1983).

The effect on ulcerations, e.g. ocular ulcerations, is determined e.g. in the rabbit by measuring the reduction of corneal ulceration following an alkali burn to the cornea.

Moreover, the invention relates to the use of a compound formula I



(a) wherein Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₁₀-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy) lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl or N-acyl(hexahydroazepinyl, piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, C₅-C₁₀-thiacycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-

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oxacycloalkyl, (amino, mono- or dialkylamino or acylamino)-C₅-C₁₀-cycloalkyl, 2-oxo(pyrrolidinyl, piperidyl or hexahydroazepinyl);
R₂ is hydrogen or lower alkyl; or

(b) wherein R and R₁ together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a); or

(c) wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by lower alkyl; oxo-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof; (for the manufacture of a medicament) for the treatment of conditions which are responsive to inhibition of macrophage metalloelastase activity, or for the treatment of atherosclerosis and restenosis, or for ocular applications selected from the treatment of pterygium, keratitis, keratoconus, open angle glaucoma or retinopathies, and the use in conjunction with refractive surgery (laser or incisional) to minimize adverse effects.

Macrophage metalloelastase (MME) inhibitory activity can be determined e.g. by measuring the inhibition of the degradation of [³H]-elastin by truncated recombinant mouse macrophage metalloelastase as follows:

About 2 ng of recombinant truncated mouse macrophage metalloelastase (FASEB Journal Vol. 8, A151, 1994), purified by Q-Sepharose column chromatography is incubated with test compounds at the desired concentrations in the presence of 5 nM CaCl₂, 400 nM NaCl, [³H]elastin (60,000 cpm/tube), and 20 mM Tris, pH 8.0, at 37°C overnight. The samples are spun in a microfuge centrifuge at 12,000 rpm for 15 minutes. An aliquot of the supernatant is counted in a scintillation counter to quantitate degraded [³H]elastin. IC₅₀'s are determined from a range of concentrations of the test compounds and the percent inhibition of enzyme activity obtained. Typically, IC₅₀ values of from 1 to 10 nM or above are obtained.

Inhibiting macrophage metalloelastase which is involved in the degradation of elastin makes the compounds of the invention suitable for treating pulmonary (bronchial) disorders, e.g. emphysema. The effect of the compounds of the invention for the treatment of emphysema is determined e.g. in animal models described in American Review of Respiratory Disease 117, 1109 (1978).

Effect of the compounds of the invention on atherosclerosis: The destabilization or rupture of atherosclerotic plaques in mammals by matrix metalloproteinases is a contributing factor to acute coronary syndrome, heart attacks and strokes occurring under atherosclerotic conditions in mammals. Compounds of the invention stabilize atherosclerotic plaques (inhibit their rupture) and are thus useful in the treatment of atherosclerosis in mammals.

Atherosclerotic plaques from cholesterol-fed rabbits contain activated matrix metalloproteinases as described by Sukhova et al, Circulation 90, 1404 (1994). The inhibitory effect of compounds of the invention on matrix metalloproteinase enzyme activity in rabbit atherosclerotic plaques is determined by in situ zymography, as described by Galis et al, J. Clin. 94, 2493 (1994), and is indicative of plaque stabilization.

Effect of the compounds of the invention on restenosis: Indicative of the effect of compounds of the invention in restenosis and vascular remodeling e.g. post-angioplasty or post-atherectomy, the compounds of the invention inhibit intimal early lesion formation (at 7 and 9 days) following balloon injury in the rat ballooned carotid artery model.

Preferably, the invention relates to the use of a compound of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₁₀-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinoliny, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; or Ar is phenyl substituted by C₃-C₇-cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C₃-C₇-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino; or Ar is phenyl

substituted on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; biphenyl-lower alkyl wherein biphenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; (pyridyl, thienyl, quinolinyl or thiazolyl)-lower alkyl, trifluoromethyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; pyridyl; thienyl, biphenyl; biphenyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; hydroxy-lower alkyl; lower alkanoyloxy-lower alkyl; lower alkoxy-lower alkyl; (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R₃-CONH-lower alkyl wherein R₃ represents (di-lower

alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl- or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

(b) or wherein R and R₁ together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a);

(c) or wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxy-carbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxy-carbonyl, benzyloxy-carbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

Especially, the invention relates to the use of a compound of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₇-alkoxy, hydroxy, phenyl-lower alkoxy, C₃-C₇-cycloalkyl-lower alkoxy, lower alkoxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen; lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-,

di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinoliny, each unsubstituted or mono- or disubstituted by lower alkyl; biphenyl; biphenyl-lower alkyl; (pyridyl or thienyl)-lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl; hydroxy-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy; biphenyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; C₃-C₁₀-cycloalkyl; C₃-C₇-cycloalkyl-lower alkyl; hydroxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R₃-CONH-lower alkyl wherein R₃ represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl- or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

(b) or wherein R and R₁ together with the chain to which they are attached form a thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a);

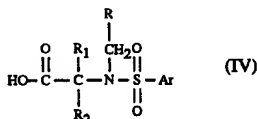
(c) or wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by

lower alkyl; oxa-cyclohexane; thia-cyclohexane; and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxy-carbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxy-carbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

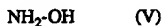
a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

In particular, the specific compounds disclosed in the examples are used according to the invention.

The compounds of formula I can be prepared e.g. by condensing a carboxylic acid of formula IV,



or a reactive functional derivative thereof, wherein R, R₁, R₂ and Ar having meaning as defined in claim 1, with hydroxylamine of formula V,



optionally in protected form, or a salt thereof;

and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, carboxyl and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, carboxyl and hydroxy groups are those that can be converted under mild conditions into free amino and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1991.

In the processes cited herein, reactive functional derivatives of carboxylic acids represent, for example, anhydrides especially mixed anhydrides, acid halides, acid azides, lower alkyl esters and activated esters thereof. Mixed anhydrides are preferably such from pivalic acid, or a lower alkyl (ethyl, isobutyl) hemiester of carbonic acid; acid halides are for example chlorides or bromides; activated esters for example succinimido, phthalimido or 4-nitrophenyl esters; lower alkyl esters are for example the methyl or ethyl esters.

Also, a reactive esterified derivative of an alcohol in any of the reactions cited herein represents said alcohol esterified by a strong acid, especially a strong inorganic acid, such as a hydrohalic acid, especially hydrochloric, hydrobromic or hydroiodic acid, or sulphuric acid, or by a strong organic acid, especially a strong organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, for example methanesulfonic acid, 4-methylbenzenesulfonic acid or 4-bromobenzenesulfonic acid. A said reactive esterified derivative is especially halo, for example chloro, bromo or iodo, or aliphatically or aromatically substituted sulfonyloxy, for example methanesulfonyloxy, 4-methylbenzenesulfonyloxy

(tosyloxy).

In the above processes for the synthesis of compounds of the invention can be carried out according to methodology generally known in the art for the preparation of hydroxamic acids and derivatives thereof.

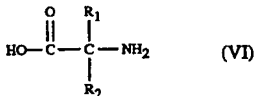
The synthesis according to the above process (involving the condensation of a free carboxylic acid of formula IV with an optionally hydroxy protected hydroxylamine derivative of formula V can be carried out in the presence of a condensing agent, e.g. 1,1'-carbonyldiimidazole, or N-(dimethylaminopropyl)-N'-ethylcarbodiimide or dicyclohexylcarbodiimide, with or without 1-hydroxybenzotriazole in an inert polar solvent, such as dimethylformamide or dichloromethane, preferably at room temperature.

The synthesis involving the condensation of a reactive functional derivative of an acid of formula IV as defined above, e.g. an acid chloride or mixed anhydride with optionally hydroxy protected hydroxylamine, or a salt thereof, in presence of a base such as triethylamine can be carried out, at a temperature ranging preferably from about -78°C to +75°C, in an inert organic solvent such as dichloromethane or toluene.

Protected forms of hydroxylamine (of formula V) in the above process are those wherein the hydroxy group is protected for example as a t-butyl ether, a benzyl ether or tetrahydropyranyl ether. Removal of said protecting groups is carried out according to methods well known in the art, e.g. hydrogenolysis or acid hydrolysis. Hydroxylamine is preferably generated in situ from a hydroxylamine salt, such as hydroxylamine hydrochloride.

The starting carboxylic acids of formula IV can be prepared as follows:

An amino acid of formula VI

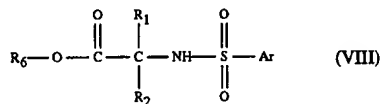


wherein R₁ and R₂ have meaning as defined herein, is first esterified with a lower alkanol,

e.g. methanol, in the presence of e.g. thionyl chloride to obtain an aminoester which is treated with a reactive functional derivative of the appropriate arylsulfonic acid of the formula VII



wherein Ar has meaning as defined hereinabove, e.g. with the arylsulfonyl chloride, in the presence of a suitable base such as triethylamine using a polar solvent such as tetrahydrofuran, toluene, acetonitrile to obtain a compound of the formula VIII



wherein R₁, R₂ and Ar have meaning as defined herein and R₆ is a protecting group, e.g. lower alkyl. Treatment thereof with a reactive esterified derivative of the alcohol of the formula IX



wherein R has meaning as defined herein, such as the halide, e.g. the chloride, bromide or iodide derivative thereof, in the presence of an appropriate base, such as potassium carbonate or sodium hydride, in a polar solvent such as dimethylformamide. The resulting compound corresponding to an ester of a compound of formula IV can then be hydrolyzed to the acid of formula IV, using standard mild methods of ester hydrolysis, preferably under acidic conditions.

The starting materials of formula VI, VII and IX are either known in the art, or can be prepared by methods well-known in the art or as described herein.

Optically active D-aminoacids of formula VI (the R-enantiomers) can be prepared according to methods known in the art, e.g. according to methods described in Tetrahedron Letters 28, 39 (1987), J. Am. Chem. Soc. 109, 7151 (1987) and J. Am. Chem. Soc. 110, 1547 (1988).

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures (preferably at or near the boiling point of the solvents used), and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The invention also relates to any novel starting materials and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The hydroxamic acids or carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or l-(alpha-

methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts.

Finally, acidic compounds of the invention are either obtained in the free form, or as a salt thereof.

Acidic compounds of the invention may be converted into salts with pharmaceutically acceptable bases, e.g. an aqueous alkali metal hydroxide, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit matrix-degrading metalloproteinases, and for the treatment of disorders responsive thereto, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its

sodium salt, or effervescent mixtures; and/or e) absorbants, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75 %, preferably about 1 to 50 %, of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art.

The pharmaceutical formulations contain an effective matrix-degrading metalloproteinase inhibiting amount of a compound of the invention as defined above either alone, or in combination with another therapeutic agent, e.g. an anti-inflammatory agent with cyclooxygenase inhibiting activity, each at an effective therapeutic dose as reported in the art. Such therapeutic agents are well-known in the art.

Examples of antiinflammatory agents with cyclooxygenase inhibiting activity are diclofenac sodium, naproxen, ibuprofen, and the like.

In conjunction with another active ingredient, a compound of the invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 25 and 250 mg of the active ingredient.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art. The concentration for $[\alpha]_D$ determinations is expressed in mg/ml.

Example 1: The following compounds for which, surprisingly, the new use of treating conditions which are responsive to inhibition of macrophage metalloelastase activity as well as treating atherosclerosis and restenosis as well as treating ocular conditions selected from pterygium, keratitis, keratoconus, open angle glaucoma and retinopathies as well as applying them in conjunction with refractive surgery (laser or incisional) to minimize adverse effects has been found are already disclosed in EP-A-606 046:

(a) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, the hydrochloride, the L-tartaric acid salt, the methanesulfonic acid salt and the maleic acid salt thereof,

(b) N-Hydroxy-2(S)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride,

(c) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-4-methylpentanamide hydrochloride,

(d) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino]-4-methylpentanamide,

(e) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](piperonyl)amino]-4-methylpentanamide,

- (f) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picoly)]amino]-4-methylpentanamide,
- (g) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picoly)]amino]-3-methylbutanamide hydrochloride,
- (h) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoly)]amino]-4,4-dimethylpentanamide hydrochloride,
- (i) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoly)]amino]-2-cyclohexylacetamide hydrochloride,
- (j) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoly)]amino]-3-methylbutanamide hydrochloride,
- (k) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picoly)]amino]-3-methylbutanamide hydrochloride,
- (l) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoly)]amino]-3-methylbutanamide hydrochloride,
- (m) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picoly)]amino]-2-cyclohexylacetamide hydrochloride,
- (n) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)]amino]-2-cyclohexylacetamide hydrochloride,
- (o) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)]amino]-2-cyclohexylacetamide hydrochloride,
- (p) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)]amino]-4-methylpentanamide,
- (q) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)]amino]-2-phenylacetamide,
- (r) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)]amino]-2-t-butylacetamide,

- (s) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]-4-methylpentanamide,
- (t) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-3-methylbutanamide,
- (u) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-4,4-dimethylpentanamide,
- (v) N-Hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-3-hydroxypropanamide,
- (w) N-hydroxy-3-[4-methoxybenzenesulfonyl]-5,5-dimethylthiazolidine-4(S)-carboxamide,
- (x) N-hydroxy-1-[4-methoxybenzenesulfonyl]-pyrrolidine-2(S)-carboxamide,
- (y) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-morpholino)ethyl]acetamide,
- (z) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[2-(4-morpholino)ethyl]acetamide,
- (aa) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride,
- (ab) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride,
- (ac) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[2-(4-morpholino)ethyl]acetamide dihydrochloride,
- (ad) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-(4-thiomorpholino)ethyl]acetamide,
- (ae) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[2-methylthiazol-4-ylmethyl]acetamide,

- (af) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[6-chloropiperonyl]-acetamide,
- (ag) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-pyrazolyl)methyl]-acetamide,
- (ah) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picoly)amino]-2-[3-picoly]acetamide dihydrochloride,
- (ai) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (aj) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (ak) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picoly)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (al) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picoly)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (am) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-methylthiazol-4-ylmethyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (an) N-hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]-2-[(1-methyl-4-imidazolyl)methyl]acetamide hydrochloride,
- (ao) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]propionamide,
- (ap) methyl 2-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionate.
- (aq) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-thiomethylbutyramide,
- (ar) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-4-(methylsulfonyl)-butyramide,

(as) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-propionamide,

(at) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-benzylacetamide,

(au) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-
6-(N,N-dimethylamino)-hexanamide hydrochloride,

(av) N-hydroxy-2-(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-
6-(N,N-dimethylamino)-hexanamide dihydrochloride,

(aw) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-picolyl)amino]-
6-(N,N-dimethylamino)-hexanamide dihydrochloride,

(ax) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-6-[(N,N-dimethyl-
glycyl)amino]hexanamide hydrochloride,

(ay) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-
tetrahydrothiopyran,

(az) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-
tetrahydropyran,

(ba) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)-
amino]-cyclohexane,

(bb) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](benzyl)amino]-
cyclopentane,

(bc) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-
cyclohexane,

(bd) 1-[N-hydroxy-carbamoyl]-1-[[4-methoxybenzenesulfonyl](3-picolyl-
amino)-cyclopropane hydrochloride,

(be) 4-[N-hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-

1-[benzyl]-piperidine,

(bf) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[dimethylaminoacetyl]-piperidine hydrochloride,

(bg) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[3-picolyl]-piperidine dihydrochloride,

(bh) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[carbomethoxymethyl]-piperidine hydrochloride,

(bi) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-piperidine trifluoroacetate;

(bj) 4-[N-Hydroxy-carbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[t-butoxycarbonyl]-piperidine;

(bk) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)-amino]-1-[methylsulfonyl]-piperidine;

(bl) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[methyl]piperidine hydrochloride,

(bm) 4-[N-Hydroxycarbamoyl]-4-[[methoxybenzenesulfonyl](benzyl)amino]-1-[morpholinocarbonyl]piperidine,

(bn) 4-[N-Hydroxycarbamoyl]-4-[[4-methoxybenzenesulfonyl](benzyl)amino]-1-[4-picolyl]piperidine dihydrochloride,

(bo) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]acetamide,

(bp) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isobutyl)amino]acetamide,

(bq) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexylmethyl)amino]acetamide,

(br) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](cyclohexyl)amino]acetamide,

(bs) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](phenethyl)amino]acetamide,

(bt) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-methylbutyl)amino]acetamide,

(bu) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](sec-butyl)amino]acetamide,

(bv) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](tert-butyl)amino]acetamide,

(bw) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-fluorobenzyl)amino]acetamide,

(bx) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-chlorobenzyl)amino]acetamide,

(by) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](isopropyl)amino]acetamide,

(bz) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methylbenzyl)amino]acetamide,

(ca) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-phenyl-1-propyl)amino]acetamide

(cb) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbutyl)amino]acetamide,

(cc) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-cyclohexylethyl)amino]acetamide,

(cd) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]acetamide

(ce) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2,2,2-trifluoroethyl)amino]acetamide,

(cf) N-Hydroxy-2-[[benzenesulfonyl](isobutyl)amino]acetamide,

(cg) N-Hydroxy-2-[[4-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide,

(ch) N-Hydroxy-2-[[4-chlorobenzenesulfonyl](isobutyl)amino]acetamide,

(ci) N-Hydroxy-2-[[4-methylbenzenesulfonyl](isobutyl)amino]acetamide,

(cj) N-Hydroxy-2-[[4-fluorobenzenesulfonyl](isobutyl)amino]acetamide,

- (ck) N-Hydroxy-2-[[benzenesulfonyl](benzyl)amino]acetamide,
- (cl) N-Hydroxy-2-[[4-nitrobenzenesulfonyl](isobutyl)amino]acetamide,
- (cm) N-Hydroxy-2-[[4-(tert)-butylbenzenesulfonyl](isobutyl)amino]acetamide,
- (cn) N-Hydroxy-2-[[4-methylsulfonylbenzenesulfonyl](isobutyl)amino]acetamide,
- (co) N-Hydroxy-2-[[3-trifluoromethylbenzenesulfonyl](isobutyl)amino]acetamide,
- (cp) N-Hydroxy-2-[[2,4,6-trimethylbenzenesulfonyl](isobutyl)amino]acetamide,
- (cq) N-Hydroxy-2-[[2,5-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide,
- (cr) N-Hydroxy-2-[[3,4-dimethoxybenzenesulfonyl](isobutyl)amino]acetamide,
- (cs) N-Hydroxy-2-[[2,4,6-triisopropylbenzenesulfonyl](isobutyl)amino]acetamide,
- (ct) N-Hydroxy-2-[[3,5-dimethylisoxazole-4-sulfonyl](benzyl)amino]acetamide,
- (cu) N-Hydroxy-2-[[2,4-dimethylthiazole-5-sulfonyl](benzyl)amino]acetamide,
- (cv) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-methoxybenzyl)amino]acetamide,
- (cw) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-picolyl)amino]acetamide,
- (cx) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](3-picolyl)amino]acetamide,
- (cy) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](piperonyl)amino]acetamide,
- (cz) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-piperidinyethyl)amino]acetamide,
- (da) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](2-quinolinylmethyl)amino]acetamide,
- (db) N-Hydroxy-2-[[4-methoxybenzenesulfonyl](4-picolyl)amino]acetamide

hydrochloride,

(dc) N-hydroxy-2-[[4-methoxybenzenesulfonyl](6-chloropiperonyl)amino] acetamide,

(dd) N-hydroxy-2-[[4-methoxybenzenesulfonyl](3,4,5-trimethoxybenzyl)-amino]acetamide,

(de) N-hydroxy-2-[[4-methoxybenzenesulfonyl](3-methoxybenzyl)amino]acetamide,

(df) N-hydroxy-2-[[4-methoxybenzenesulfonyl](2-[4-morpholino]ethyl)amino]acetamide,

(dg) N-Hydroxy-2-[[4-aminobenzenesulfonyl](isobutyl)amino]acetamide,

(dh) N-Hydroxy-2-[[4-dimethylaminobenzenesulfonyl](isobutyl)amino]acetamide,

(di) N-hydroxy-2-[[4-hexyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dj) N-Hydroxy-2-[[4-ethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(dk) N-Hydroxy-2-[[4-butyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dl) N-Hydroxy-2-[[4-(3-methyl)butyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dm) N-Hydroxy-2-[[4-heptyloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dn) N-Hydroxy-2-[[4-(cyclohexylmethoxy)benzenesulfonyl](isobutyl)amino]acetamide,

(do) N-Hydroxy-2-[[4-isopropylloxybenzenesulfonyl](isobutyl)amino]acetamide,

(dp) N-Hydroxy-2-[[4-ethoxyethoxybenzenesulfonyl](isobutyl)amino]acetamide,

(dq) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(2-methyl-5-tetrazolyl)methyl]acetamide,

(dr) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(1-methyl-5-tetrazolyl)-methyl]acetamide,

(ds) N-hydroxy-2-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-[(5-tetrazolyl)-methyl]acetamide,

(dt) N-hydroxy-2-[[4-methoxybenzenesulfonyl](4-phenylbenzyl)amino]-2-[(5-tetrazolyl)-methyl]acetamide,

(du) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide, and the hydrochloride thereof,

(dv) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide and the hydrochloride thereof,

(dw) N-(benzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(dx) N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(dy) N-(4-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide,

(dz) N-(2,4-dimethoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(ea) N-(2-methoxybenzyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl-butanamide,

(eb) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3(R)-(3-picolyl-oxy)-butanamide dihydrochloride,

(ec) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-picolyl)amino]-2-cyclohexylacetamide hydrochloride,

(ed) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-(2-pyridyl)ethyl)amino]-2-cyclohexylacetamide,

(ee) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-(3-pyridyl)propyl)-amino]-2-cyclohexylacetamide,

(ef) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](2-methyl-pyrid-5-ylmethyl)-amino]-2-cyclohexylacetamide,

(eg) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](4-tetrahydropyranmethyl)-amino]-2-cyclohexylacetamide

(eh) N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](benzyl)amino]-2-(4-N-methylpiperidiny)acetamide hydrochloride.

It is to be understood that each compound mentioned in example 1 may be used either in the neutral form, or in the form of a pharmaceutically acceptable salt, e.g. in the specific salt form mentioned in the above list.

Reference example A (corresponds to example 1(a) of EP-A-606 046):

(a) N-(t-Butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide (4.1 g, 9.13 mmol) is dissolved in dichloroethane (150 mL) containing ethanol (0.53ml, 9.13 mmol) in a round bottom flask, and the reaction is cooled to -10°C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 30 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for 2 days. The solvent is reduced to 1/3 volume by evaporation and triturated with ether. The mixture is filtered, filter cake removed, and dried in vacuo to provide N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide hydrochloride as a white solid, m.p. 169-170°C (dec).

The starting material is prepared as follows:

(b) To a solution of D-valine (15.0 g, 128.0 mmol) in 1:1 dioxane/ water (200 mL) containing triethylamine (19.4 g, 192.0 mmol) at room temperature is added 4-methoxybenzenesulfonyl chloride (29.0 g, 141.0 mmol), and the reaction mixture is stirred at room temperature overnight. The mixture is then diluted with methylene chloride, washed with 1N aqueous hydrochloric acid and water. The organic layer is washed again with brine,

dried (Na_2SO_4), and the solvent is evaporated to provide N-[4-methoxybenzenesulfonyl]-(D)-valine as a crude product. A solution of this crude product (15.0 g) in toluene (100 mL) containing N,N-dimethylformamide di-t-butyl acetal (50 mL, 206.5 mmol) is heated to 95°C for 3 hours. The solvent is then evaporated. The crude product is purified by silica gel chromatography (30% ethyl acetate/hexanes) to provide N-[4-methoxybenzenesulfonyl]-(D)-valine t-butyl ester.

(c) To a solution of N-[4-methoxybenzenesulfonyl]-(D)-valine t-butyl ester (4.38 g, 13.0 mmol) in dimethylformamide (200 mL) is added 3-picolyl chloride hydrochloride (2.3 g, 14.0 mmol) followed by potassium carbonate (17.94 g, 130.0 mmol). The reaction mixture is stirred at room temperature for 2 days. The mixture is then diluted with water and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (ethyl acetate) to give t-butyl 2(R)-[N-[4-methoxybenzenesulfonyl]-(3-picolyl)amino]-3-methylbutanoate.

(d) t-Butyl 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoate (5.3 g, 12.2 mmol) is dissolved in methylene chloride (150 mL) and cooled to -10°C . Hydrochloric acid gas is bubbled into the solution for 10 minutes. The reaction mixture is then sealed, warmed to room temperature and stirred for 4 hours. The solvent is then evaporated to provide 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanoic acid hydrochloride.

(e) 2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methyl butanoic acid hydrochloride (5.0 g, 12.06 mmol), 1-hydroxybenzotriazole (1.63 g, 12.06 mmol), 4-methylmorpholine (6.6 mL, 60.31 mmol), and O-t-butylhydroxylamine hydrochloride (54.55 g, 36.19 mmol) are dissolved in methylene chloride (200 mL). N-[Dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (3.01 g, 15.68 mmol) is added, and the reaction is stirred overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (2% methanol/methylene chloride) to give N-(t-butyloxy)-2(R)-[[4-methoxybenzenesulfonyl](3-picolyl)amino]-3-methylbutanamide.

Reference example B (corresponds to example 32 of EP-A-606 046):

(a) N-(t-Butyloxy)-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidiny)acetamide (733.0 mg, 1.46 mmol) is dissolved in methylene chloride (60 mL) containing ethanol (67.0 mg, 1.46 mmol), and the reaction is cooled to -10°C. Hydrochloric acid gas (from a lecture bottle) is bubbled through for 15 minutes. The reaction is sealed, allowed to slowly warm to room temperature, and stirred for 6 days. The solvent is reduced to 1/3 volume by evaporation and triturated with ether. The mixture is filtered, filter cake removed, and dried in vacuo to provide N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidiny)acetamide hydrochloride as a light tan solid, m.p. >160°C (dec).

The starting material is prepared as follows:

(b) To a solution of ethyl 4-pyridylacetate (11.17 g, 67.62 mmol) in 2N hydrochloric acid (100 mL) is added platinum (IV) oxide (275 mg). The mixture is shaken in a Parr hydrogenation apparatus for 60 hours under a hydrogen pressure of 50 psi (= 3.45 bar). The reaction mixture is basified to pH 8-9 with saturated aqueous sodium carbonate and then washed with methylene chloride. The aqueous layer is concentrated in vacuo providing sodium 4-piperidyl acetate as a white solid. To a solution of the crude product (5.0 g, 30.3 mmol) in 3:1 water/dioxane (200 mL) at 0°C is added a solution of di-tert-butylidicarbonate (6.38 g, 29.3 mmol) in dioxane (25 mL) in one portion. The cloudy reaction mixture is warmed to room temperature and stirred overnight. The mixture is then filtered, cooled to 0°C and acidified with cold 6N hydrochloric acid (pH=2-3). This solution is extracted with ethyl acetate. The combined organic layers are dried (Na₂SO₄), and the solvent is evaporated to provide N-t-BOC-piperidine-4-acetic acid as a white crystalline solid.

(c) To a solution of N-t-BOC-piperidine-4-acetic acid (4.67 g, 19.22 mmol) in tetrahydrofuran at -78°C is added triethylamine (2.53 g, 24.99 mmol) followed by pivaloyl chloride (2.55 g, 21.14 mmol). The resulting white slurry is stirred at -78°C for 15 minutes, warmed to 0°C for 45 minutes, then recooled to -78°C. In a separate flask, (R)-(+)-4-benzyl-2-oxazolidinone (4.09 g, 23.1 mmol) is dissolved in tetrahydrofuran (50 mL) and 1 M n-butyl lithium in hexanes (14.4 mL, 23.06 mmol) is added dropwise at -78°C. The solution is added via cannula to the aforementioned white slurry at -78°C. The reaction mixture is stirred at -78°C for 15 minutes, then warmed to room temperature over 2.5 hours. The mixture is quenched with saturated aqueous sodium carbonate and the tetrahydrofuran is evaporated in vacuo. The remaining aqueous layer is diluted with water

and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated under vacuum. The product is purified by silica gel chromatography (75% to 50% hexane/ethyl acetate) to give 3-[2-(N-t-BOC-4-piperidiny)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone.

(d) To a solution of 3-[2-(N-t-BOC-4-piperidiny)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone (7.54 g, 18.76 mmol) in tetrahydrofuran (175 mL) at -78°C is added a 0.5 M solution of potassium bis(trimethylsilylamide) in toluene (37.5 mL, 18.76 mmol) dropwise. After stirring for 20 minutes at -78°C , a pre-cooled solution of trisylazide (7.25 g, 23.4 mmol) in tetrahydrofuran (55 mL) is added via cannula at -78°C . The mixture is stirred for 15 minutes at -78°C , then acetic acid 3.38 g, 56.28 mmol) is added followed by immediate warming to room temperature through immersion in a water bath. The reaction mixture is stirred for 1.5 hours at room temperature. The tetrahydrofuran is removed under vacuum and the resulting residue is partitioned between saturated aqueous sodium carbonate and ethyl acetate. The aqueous layer is removed and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The product is purified by silica gel chromatography (30% to 50% ethyl acetate/hexanes) to give 3-[2-(R)-azido-2-(N-t-BOC-4-piperidiny)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone.

(e) To a solution of 3-[2-(R)-azido-2-(N-t-BOC-4-piperidiny)-1-oxoethyl]-4(R)-(benzyl)-2-oxazolidinone (5.84 g, 13.17 mmol) in 3:1 tetrahydrofuran/water/200 mL) at 0°C is added 30% aqueous hydrogen peroxide (5.12 mL, 52.67 mmol) followed by lithium hydroxide monohydrate (1.11 g, 26.34 mmol). The reaction mixture is stirred at 0°C for 1 hour. The mixture is quenched by addition of sodium sulfite (7.1 g) at 0°C . The tetrahydrofuran is removed in vacuo and the remaining aqueous layer is further diluted with water. This aqueous layer is then washed with methylene chloride and acidified with 1N hydrochloric acid. The resulting acidic aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried (Na_2SO_4) and concentrated in vacuo to provide crude 2-(R)-azido-2-(N-t-BOC-4-piperidiny)acetic acid.

(f) To a pre-stirred solution of tin (II) chloride (3.14 g, 16.55 mmol) in methanol (100 mL) at 0°C is added 2-(R)-azido-2-(N-t-BOC-4-piperidiny)acetic acid (2.35 g, 8.27 mmol) in methanol (25 mL) dropwise. The reaction mixture is stirred at 0°C for 10 minutes then warmed to room temperature overnight. The methanol is removed in vacuo to provide crude R-(N-t-BOC-4-piperidiny) glycine, which is used directly in the next reaction

without purification. The crude product from the above reaction is dissolved in 2:1 dioxane/water (120 mL) and triethylamine (7.53 g, 74.43 mmol) and cooled to 0°C. To this mixture is added 4-methoxybenzenesulfonyl chloride (2.22 g, 10.75 mmol) and then the reaction mixture is warmed to room temperature overnight. The dioxane is removed in vacuo and the residue is partitioned between dilute aqueous sodium bicarbonate and ethyl acetate. The basic aqueous layer is removed, acidified with 1 N hydrochloric acid, and extracted with ethyl acetate. The resulting emulsion is passed through a celite pad washing with ethyl acetate. The organic filtrate is dried (Na_2SO_4) and concentrated in vacuo to provide 2(R)-[(4-methoxybenzenesulfonyl)amino]-2-(N-t-BOC-4-piperidinyl) acetic acid as crude product.

(g) A solution of crude 2(R)-[(4-methoxybenzenesulfonyl)amino]-2-(N-t-BOC-4-piperidinyl)-acetic acid (2.88 g) in dimethylformamide (60 mL) containing N,N-dicyclohexylamine (1.22 g, 6.73 mmol) and benzyl bromide (1.15 g, 6.73 mmol) is stirred at room temperature for 3.5 hours. To this same reaction mixture is again added benzyl bromide (1.26 g, 7.4 mmol) followed by potassium carbonate (6.5 g, 47.11 mmol). The reaction mixture is stirred over the weekend at room temperature. The mixture is diluted with water and extracted with ethylacetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product is purified by silica gel chromatography (15% to 25% ethyl acetate/hexanes) to provide benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)-amino]-2-(N-t-BOC-4-piperidinyl)acetate.

(h) A solution of benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(N-t-BOC-4-piperidinyl) acetate (2.0 g, 3.3 mmol) in dichloromethane (50 mL) is cooled to 0°C and hydrochloric acid gas (from a lecture bottle) is bubbled through for 10 minutes. The reaction mixture is warmed to room temperature over 30 minutes. The solvent is removed in vacuo to yield benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)-amino]-2-(N-t-BOC-4-piperidinyl) acetate hydrochloride as a white foam.

(i) To a solution of benzyl 2(R)-[(4-methoxybenzene sulfonyl)(benzyl)amino]-2-(N-t-BOC-4-piperidinyl) acetate hydrochloride salt (1.28 g, 2.35 mmol) heated to reflux is added sodium formate (480.0 mg, 7.06 mmol) and formaldehyde (0.57 mL, 7.06 mmol). The reaction mixture is refluxed for 10 minutes, then two additional aliquots of formaldehyde (0.57 mL, 7.06 mmol) are added at 10 minute intervals. The reaction mixture is refluxed for an additional 3 hours. The formic acid is removed in vacuo and the

residue is partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The basic aqueous layer is further extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4) and concentrated in vacuo to provide benzyl 2(R)-[(4-methoxybenzenesulfonyl)benzylamino]-2-(4-N-methylpiperidinyl) acetate as a crude product. A solution of this crude product (1.23 g) in 3N HCl (40 mL) is refluxed at 120°C for 2 days. The mixture is concentrated in vacuo to provide acid as a crude product. To a solution of this crude product (1.08 g) in methylene chloride (75 mL) is added 1-hydroxybenzotriazole (0.312 g, 2.31 mmol), 4-methylmorpholine (1.64 g, 16.17 mmol), O-t-butylhydroxylamine hydrochloride (870.0 mg, 6.93 mmol), followed by N-[dimethylaminopropyl]-N'-ethylcarbodiimide hydrochloride (576.0 mg, 3.0 mmol). The reaction mixture is stirred at room temperature overnight. The reaction is then diluted with water and extracted with methylene chloride. The combined organic extracts are washed with brine, dried (Na_2SO_4), and the solvent is evaporated. The crude product is purified by silica gel chromatography (3% to 7% methanol/methylene chloride containing 0.5% ammonium hydroxide) to give N-(t-butyloxy)-2(R)-[(4-methoxybenzenesulfonyl)-(benzyl)amino]-2-(4-N-methylpiperidinyl)acetamide.

Example 2: (a) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[N-(dimethylaminoacetyl)-4-piperidinyl]acetamide, m.p. 130-150°C, is prepared similarly as N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-N-methylpiperidinyl)acetamide hydrochloride [see reference example B or EP-A-606 046, example 32, pages 34-35].

The required intermediate is prepared as follows:

To benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-piperidinyl)acetate [0.866 g, obtained by splitting off the BOC group in the product of reference example B(g) in a usual manner, e.g. by treatment with HCl gas] in methylene chloride (50 ml) is added N,N-dimethylglycine (0.172 g), N-methylmorpholine (0.7 ml), 1-hydroxybenzotriazole (0.215 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.610 g). The mixture is stirred at room temperature over the weekend, diluted with water and extracted with methylene chloride. The combined organic extracts are dried over Na_2SO_4 and evaporated to dryness to yield benzyl 2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2[(N-dimethylaminoacetyl)-4-piperidinyl]acetate. This benzyl ester is converted to the corresponding acid e.g. by hydrogenation in the presence of Pd/C. Conversion of the acid to the BOC-protected hydroxamic acid is accomplished as described in reference example

B(i). The BOC group is removed as described in reference example A(a).

(b) Similarly prepared - see in particular reference example B(c) to (i) and reference example A(a) - is also N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(3-pyrrolidinyl)-acetamide hydrochloride, m.p. 160°C dec., starting with N-t-butoxycarbonyl-3-pyrrolidineacetic acid.

(c) Similarly prepared - see in particular reference example B(c) to (i) and reference example A(a) - is also N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(N-t-butoxycarbonyl-3-pyrrolidinyl)-acetamide, m.p. 120°C dec., starting with N-t-butoxycarbonyl-3-pyrrolidineacetic acid.

(d) Similarly prepared - see in particular reference example B and reference example A(a) - is also N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picoly)amino]-2-(4-tetrahydropyranyl)-acetamide hydrochloride, m.p. >152°C dec. starting with tetrahydropyranyl-4-acetic acid.

Example 3: Prepared similarly to the reference examples A and B (as well as the examples 1-32 of EP-A-606 046) - in particular reference example A - is N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(3-picoly)amino]-2-(trans-4-hydroxycyclohexyl)-acetamide hydrochloride, m.p. 130-155°C.

The starting material is prepared as follows:

D-4-hydroxyphenylglycine (10 g) is dissolved in 3N sodium hydroxide (20 ml). Water (180 ml) and then Raney nickel (27 g) are added. The reaction mixture is hydrogenated at about 3 atmospheres pressure [= 3.04 bar] and 50-80°C overnight.

The reaction mixture is filtered and reduced in volume to about 85 ml and dioxane (85 ml) is added. The solution of 4-hydroxycyclohexylglycine (see Coll. Czech. Chem. Comm. 49, 712-742 (1984)) is cooled to 0°C and treated with triethylamine (11.37 ml) and 4-methoxybenzenesulfonyl chloride (10.95 g). The reaction mixture is allowed to warm to room temperature and stirred over the weekend. The dioxane is removed in vacuo and the remaining aqueous solution is diluted with 1N hydrochloride acid. The resulting precipitate is collected, washed with water and ether to yield (R)-N-(4-methoxybenzenesulfonyl)-4-hydroxycyclohexylglycine which is converted to the methyl ester with

methanol in the presence of thionyl chloride. To a solution of (R)-N-(4-methoxybenzenesulfonyl)-4-hydroxycyclohexylglycine methyl ester (0.859 g) in methylene chloride (8 ml) are added acetic anhydride (2.26 ml) and pyridine (3.90 ml). The reaction mixture is stirred at room temperature overnight, quenched with methanol, washed with 1N hydrochloric acid and extracted with methylene chloride. The methylene chloride extract is dried over sodium sulfate and evaporated to dryness to yield (R)-N-(4-methoxybenzenesulfonyl)-4-acetyloxycyclohexylglycine methyl ester. Heating with 3 NHCl at reflux for 24 hours yields (R)-N-(4-methoxybenzenesulfonyl)-4-hydroxycyclohexylglycine.

Example 4: Prepared similarly to the reference examples A and B and examples 2-3 (as well as the examples 1-32 of EP-A-606 046) are:

(a) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(trans-4-dimethylaminocyclohexyl)acetamide hydrochloride, m.p. 138-146°C (see in particular reference example A).

The starting material is prepared as follows:

A solution of oxalyl chloride (1.25 g) in methylene chloride (30 ml) is cooled to -78°C and dimethylsulfoxide (1.16 ml) is slowly added. The reaction mixture is stirred at -78°C for about 30 minutes and a solution of (R)-N-(4-methoxybenzenesulfonyl)-4-hydroxycyclohexylglycine methyl ester (2.34 g) in methylene chloride (30 ml) is added dropwise. Stirring is continued for 30 minutes at -78°C and then at 0°C for 30 minutes. The reaction mixture is again cooled to -78°C, triethylamine (7.3 ml) is added dropwise, and the reaction mixture is stirred at -78°C for 30 minutes, allowed to warm to room temperature over an hour, diluted with methylene chloride, washed first with 1N hydrochloric acid and then brine. The organic layer is dried over sodium sulfate, evaporated to dryness, and the resulting product is purified by flash chromatography using 50-60% ethyl acetate in hexane to yield (R)-N-(4-methoxybenzenesulfonyl)-4-oxocyclohexylglycine methyl ester as a white solid. Treatment with benzyl bromide in DMF in the presence of potassium carbonate at room temperature yields (R)-N-(4-methoxybenzenesulfonyl)-N-benzyl-4-oxocyclohexylglycine methyl ester as an oil. The ketone (2.2 g) is dissolved in methylene chloride (3 ml) and isopropanol (60 ml). Molecular sieves (3A°, 1.5 g), sodium cyanoborohydride (0.311 g), and ammonium acetate (3.81 g) are added. The reaction mixture is stirred at room temperature overnight, filtered and evaporated to dryness. The residue is partitioned between water and methylene chloride and the product extracted

with methylene chloride. The resulting product is purified by flash chromatography using methanol/methylene chloride/0.5% ammonium hydroxide as eluent to yield (R)-N-(4-methoxybenzenesulfonyl)-N-benzyl-4-aminocyclohexylglycine methyl ester. N-Methylation with formic acid/formaldehyde/sodium formate at reflux temperature followed by hydrolysis with 3N hydrochloric acid at reflux temperature yields 2-(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(trans-4-dimethylaminocyclohexyl)-acetic acid.

(b) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[trans-4-(dimethylaminoacetyl)amino]cyclohexyl]acetamide hydrochloride, m.p. 163-170°C, obtained from (R)-N-(4-methoxybenzenesulfonyl)-N-benzyl-4-aminocyclohexylglycine benzyl ester, which is in turn prepared from (R)-N-(4-methoxybenzenesulfonyl)-4-hydroxycyclohexylglycine benzyl ester (see in particular example 2(a) and reference example A).

Example 5: Prepared similarly to the reference examples A and B and examples 2-4 (as well as the examples 1-32 of EP-A-606 046) are:

(a) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-tetrahydrofuranyl)-acetamide, m.p. 89-92°C, $[\alpha]_D^{25} + 4.82$ (c 8, CH₃OH).

The starting material, R-(2-tetrahydrofuranyl)-glycine, is prepared according to J. Am. Chem. Soc. 110 (1988) 1547.

(b) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(3-picolyl)amino]-2-(2-tetrahydrofuranyl)-acetamide, m.p. 91-93°C, $[\alpha]_D^{25} + 0.62$ (c 7.0, CH₃OH);

(c) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-tetrahydrofuranyl)-acetamide, m.p. 143-144°C; $[\alpha]_D^{25} + 1.03$ (c 6.4, CH₃OH);

(d) N-hydroxy-2(S)-[(4-methoxybenzenesulfonyl)(3-picolyl)amino]-2-(2-tetrahydrofuranyl)-acetamide, m.p. 162-163°C; $[\alpha]_D^{25} - 4.22$ (c 6.5, CH₃OH);

(e) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(trans-4-hydroxy-2-tetrahydrofuranyl)acetamide, m.p. 53-56°C, as a mixture of diastereoisomers; the starting material, trans-(4-hydroxy-2-tetrahydrofuranyl)glycine is prepared according to J.

Am. Chem. Soc. 110 (1988) 4533;

(f) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(4-oxacyclooctyl)acetamide, m.p. 152-157°C, as a mixture of diastereoisomers;

(g) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)-amino]-2-(4-oxacycloheptyl)acetamide hydrochloride, m.p. 130-145°C, as a mixture of diastereoisomers;

(h) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-cyclooctylacetamide hydrochloride, m.p. 124-140°C;

(i) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-oxohexahydroazepin-5-yl)acetamide hydrochloride, diastereoisomer A, m.p. 160-172°C dec.

(j) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(2-oxohexahydroazepin-5-yl)acetamide hydrochloride, diastereoisomer B, m.p. 155-170°C;

(k) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-oxohexahydroazepin-5-yl)acetamide, diastereoisomer A, m.p. 115-130°C;

(l) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-(2-oxohexahydroazepin-5-yl)acetamide, diastereoisomer B, m.p. 120-140°C;

(m) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3,4-dimethoxybutanamide, m.p. 53-55°C;

(n) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(n-propyl)amino]-3-methoxy-3-(N-tert-butoxycarbonyl-4-piperidyl)propionamide, m.p. 102-103°C;

(o) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(N-ethoxycarbonyl-4-piperidyl)-acetamide hydrochloride, m.p. 145-158° (dec.); $[\alpha]_D^{25} = +19.83$ (c=5.56 mg/ml, methanol);

(p) N-hydroxy-2-[(4-methoxybenzenesulfonyl)(4-picolyl)amino]-2-(tetrahydro-2H-pyran-2-yl)-acetamide hydrochloride, diastereoisomer A, m.p. 169-170° (dec.);

(q) N-hydroxy-2-[(4-methoxybenzenesulfonyl)(4-picoly)amino]-2-(tetrahydro-2H-pyran-2-yl)-acetamide hydrochloride, diastereoisomer B, m.p. 158-161° (dec.);

(r) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picoly)amino]-2-(cis-4-hydroxy-cyclohexyl)-acetamide hydrochloride, m.p. 175-180°, $[\alpha]_D^{25} = +14.04$ (c=6.37 mg/ml, methanol);

(s) N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(benzyl)amino]-2-[trans-4-(ethoxycarbonylamino)cyclohexyl]-acetamide, m.p. 105-115°.

Example 6: Preparation of 3000 capsules each containing 25 mg of the active ingredient, for example, a compound mentioned in one of the examples 1-5:

Active ingredient	75.00 g
Lactose	750.00 g
Avicel PH 102	300.00 g
(microcrystalline cellulose)	
Polyplasdone XL	30.00 g
(polyvinylpyrrolidone)	
Purified water	q.s.
Magnesium stearate	9.00 g

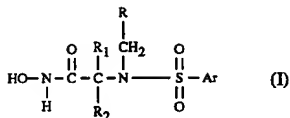
The active ingredient is passed through a No. 30 hand screen.

The active ingredient, lactose, Avicel PH 102 and Polyplasdone XL are blended for 15 minutes in a mixer. The blend is granulated with sufficient water (about 500 mL), dried in an oven at 35°C overnight, and passed through a No. 20 screen.

Magnesium stearate is passed through a No. 20 screen, added to the granulation mixture, and the mixture is blended for 5 minutes in a mixer. The blend is encapsulated in No. 0 hard gelatin capsules each containing an amount of the blend equivalent to 25 mg of the active ingredient.

Claims

1. A compound of formula I



wherein

Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is C₈-C₁₀-cycloalkyl, (N-acyl-piperidyl)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy)-lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl), N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-cycloalkyl, (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl, (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl, (amino, mono- or di-lower alkylamino or acylamino)-C₅-C₁₀-cycloalkyl, 2-oxo-(pyrrolidinyl, piperidyl or hexahydroazepinyl);

R₂ is hydrogen or lower alkyl;

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically

acceptable salt thereof.

2. A compound of formula I according to claim 1, wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₁₀-alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; or Ar is phenyl substituted by C₃-C₇-cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C₃-C₇-cycloalkyl-lower alkyl)-thio, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; biphenyl-lower alkyl wherein biphenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; (pyridyl, thienyl, quinolinyl or thiazolyl)-lower alkyl, trifluoromethyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkyl)piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is pyrrolidinyl; hexahydroazepinyl; N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl); N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl);

C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-cycloalkyl; (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl; or (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

3. A compound of formula I according to claim 1, wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₇-alkoxy, hydroxy, phenyl-lower alkoxy, C₃-C₇-cycloalkyl-lower alkoxy, lower alkyl-oxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

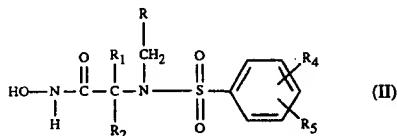
R is hydrogen; lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenyl; biphenyl-lower alkyl; (pyridyl or thienyl)-lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl; hydroxy-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkyl)piperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is pyrrolidinyl; hexahydroazepinyl; N-lower alkyl-(hexahydroazepinyl or pyrrolidinyl); N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-cycloalkyl; (hydroxy or oxo)-C₅-C₁₀-thiacycloalkyl; (hydroxy or oxo)-C₅-C₁₀-oxacycloalkyl; or (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 of formula II,



wherein

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, or (morpholino, thiomorpholino, piperidino, pyrrolidino or N-lower alkylpiperidyl)-lower alkyl;

R₁ is pyrrolidinyl, hexahydroazepinyl, N-lower alkyl-(pyrrolidinyl or hexahydroazepinyl), C₅-C₇-oxacycloalkyl, C₅-C₇-thiacycloalkyl, (hydroxy or oxo)-cyclohexyl, (amino, mono- or di-lower alkylamino)-cyclohexyl or 2-oxo-hexahydroazepinyl;

R₂ is hydrogen;

R₄ is hydrogen, lower alkoxy, hydroxy, carbocyclic or heterocyclic aryl-lower alkoxy, lower alkylthio or carbocyclic or heterocyclic aryl-lower alkylthio, lower alkyloxy-lower alkoxy, halogen, trifluoromethyl, lower alkyl, nitro or cyano;

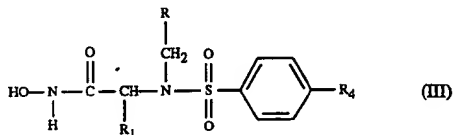
R₅ is hydrogen, lower alkyl or halogen;

or R₄ and R₅ together on adjacent carbon atoms represent methylenedioxy, ethylenedioxy,

oxyethylene or oxypropylene;

or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 of formula III,



wherein R represents lower alkyl, trifluoromethyl, C₅-C₇-cycloalkyl, (oxa or thia)-C₄-C₅-cycloalkyl, biaryl, carbocyclic monocyclic aryl or heterocyclic monocyclic aryl; R₁ represents C₅-C₇-oxacycloalkyl or (hydroxy, oxo or di-lower alkylamino)-cyclohexyl; R₄ represents lower alkoxy or carbocyclic or heterocyclic aryl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

6. A compound of formula III according to claim 5, wherein R represents heterocyclic monocyclic aryl selected from tetrazolyl, triazolyl, thiazolyl, imidazolyl and pyridyl, each unsubstituted or substituted by lower alkyl; or R represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; R₁ represents 2- or 3-tetrahydrofuranyl; and R₄ represents lower alkoxy or phenyl-lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

7. A compound of formula III according to claim 5, wherein R represents 2-, 3- or 4-pyridyl or phenyl; R₁ represents 2- or 3-tetrahydrofuranyl; and R₄ represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

8. A compound of formula III according to claim 5, wherein R is lower alkyl, 2-, 3- or 4-pyridyl or phenyl; R₁ is C₈-C₁₀-cycloalkyl, (N-lower alkoxycarbonyl-piperidyl)-(lower alkoxy)-lower alkyl, pyrrolidinyl, N-(lower

alkoxycarbonyl or di-lower alkylamino-lower alkanoyl)-(piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, hydroxy-C₅-C₁₀-cycloalkyl, (hydroxy)-C₅-C₁₀-oxacycloalkyl, (di-lower alkylamino, di-lower alkylamino-lower alkanoylamino or lower alkoxycarbonylamino)-C₅-C₁₀-cycloalkyl or 2-oxo-piperidyl; and R₄ represents lower alkoxy; or a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1-8 wherein the asymmetric carbon to which R₁ is attached is assigned the (R)-configuration.

10. A compound according to claim 1 which is N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picoly)amino]-2-(2-tetrahydrofuryl)-acetamide or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 which is N-hydroxy-2(R)-[(4-methoxybenzenesulfonyl)(4-picoly)amino]-2-(N-ethoxycarbonyl-4-piperidyl)-acetamide or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 and a pharmaceutically acceptable carrier.

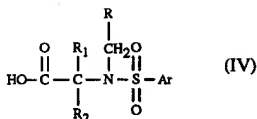
13. A compound according to any one of claims 1 to 11 for use in a method for the therapeutic treatment of the animal or human body.

14. A compound according to any one of claims 1 to 11 for use in the treatment of matrix-degrading metalloproteinase dependent conditions.

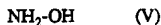
15. The use of a compound according to any one of claims 1 to 11 for the manufacture of a pharmaceutical composition for the treatment of matrix-degrading metalloproteinase dependent conditions.

16. A process for the preparation of a compound of formula I according to claim 1, which comprises condensing a carboxylic acid of formula IV,

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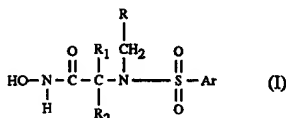
wherein R, R₁, R₂ and Ar having meaning as defined in claim 1, or a reactive functional derivative thereof, with hydroxylamine of formula V,



optionally in protected form, or a salt thereof;

and, if necessary, temporarily protecting any interfering reactive group(s), and then liberating the resulting compound of the invention; and, if required or desired, converting a resulting compound of the invention into another compound of the invention, and/or, if desired, converting a resulting free compound into a salt or a resulting salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates obtained into the single isomers or racemates; and/or, if desired, resolving a racemate into the optical antipodes.

17. Use of a compound formula I



(a) wherein Ar is carbocyclic or heterocyclic aryl;

R is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, acylamino-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl,

or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen, lower alkyl, carbocyclic aryl-lower alkyl, carbocyclic aryl, heterocyclic aryl, biaryl, biaryl-lower alkyl, heterocyclic aryl-lower alkyl, mono- or poly-halo-lower alkyl, C₃-C₁₀-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl, hydroxy-lower alkyl, acyloxy-lower alkyl, lower alkoxy-lower alkyl, (carbocyclic or heterocyclic aryl)-lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, (N-lower alkyl-piperazino or N-carbocyclic or heterocyclic aryl-lower alkylpiperazino)-lower alkyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-lower alkyl, acylamino-lower alkyl, piperidyl, (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, N-acyl or N-lower alkylpiperidyl)-(hydroxy or lower alkoxy) lower alkyl, pyrrolidinyl, hexahydroazepinyl, N-lower alkyl or N-acyl(hexahydroazepinyl, piperidyl or pyrrolidinyl), C₅-C₁₀-oxacycloalkyl, C₅-C₁₀-thiacycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl, (hydroxy- or oxo-) C₅-C₁₀-oxacycloalkyl, (amino, mono- or dialkylamino or acylamino)-C₅-C₁₀-cycloalkyl, 2-oxo(pyrrolidinyl, piperidyl or hexahydroazepinyl);

R₂ is hydrogen or lower alkyl; or

(b) wherein R and R₁ together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a); or

(c) wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by lower alkyl; oxo-cyclohexane, thia-cyclohexane, indane, tetralin, piperidine or piperidine substituted on nitrogen by acyl, lower alkyl, carbocyclic or heterocyclic aryl-lower alkyl, (carboxy, esterified or amidated carboxy)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

pharmaceutically acceptable prodrug derivatives; and pharmaceutically acceptable salts thereof; (for the manufacture of a medicament) for the treatment of conditions which are responsive to inhibition of macrophage metalloelastase activity, or for the treatment of atherosclerosis and restenosis, or for ocular applications selected from the treatment of pterygium, keratitis, keratoconus, open angle glaucoma or retinopathies, and the use in

conjunction with refractive surgery (laser or incisional) to minimize adverse effects.

18. Use according to claim 17, where the compound used is a compound of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C_1-C_{10} -alkoxy, hydroxy; phenyl-lower alkoxy wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; heterocyclic aryl-lower alkoxy wherein heterocyclic aryl is selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolynyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; or Ar is phenyl substituted by C_3-C_7 -cycloalkyl-lower alkoxy, (lower alkyl, phenyl-lower alkyl or C_3-C_7 -cycloalkyl-lower alkyl)-thio, lower alkoxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino; or Ar is phenyl substituted on adjacent carbon atoms, by C_1-C_2 -alkylenedioxy or oxy- C_2-C_3 -alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen, lower alkyl, phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(thio, sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C_1-C_2 -alkylenedioxy or oxy- C_2-C_3 -alkylene; or a heterocyclic aryl radical selected from pyridyl, tetrazolyl, triazolyl, thiazolyl, thienyl, imidazolyl and quinolynyl, each unsubstituted or mono- or disubstituted by lower alkyl or halogen; biphenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; biphenyl-lower alkyl wherein biphenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or cyano; (pyridyl, thienyl, quinolynyl or thiazolyl)-lower alkyl, trifluoromethyl, C_3-C_7 -cycloalkyl, C_3-C_7 -cycloalkyl-lower alkyl, (oxa or thia)- C_3-C_6 -cycloalkyl, [(oxa or thia)- C_3-C_6 -cycloalkyl]-lower alkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl, (amino, mono- or di-lower alkylamino)-lower alkyl, lower alkanoylamino-lower alkyl, (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; phenyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; pyridyl; thienyl, biphenyl; biphenyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; hydroxy-lower alkyl; lower alkanoyloxy-lower alkyl; lower alkoxy-lower alkyl; (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R₃-CONH-lower alkyl wherein R₃ represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl- or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

(b) or wherein R and R₁ together with the chain to which they are attached form a 1,2,3,4-tetrahydro-isoquinoline, piperidine, oxazolidine, thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a);

(c) or wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane, thia-cyclohexane, indane, tetralin and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, benzyloxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

19. Use according to claim 17, where the compound used is a compound of formula I

(a) wherein Ar is phenyl which is unsubstituted or mono-, di- or tri-substituted by C₁-C₇-alkoxy, hydroxy, phenyl-lower alkoxy, C₃-C₇-cycloalkyl-lower alkoxy, lower alkyloxy-lower alkoxy, halogen, lower alkyl, cyano, nitro, trifluoromethyl, lower alkyl-(sulfinyl or sulfonyl), amino, mono- or di-lower alkylamino or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; or Ar is thienyl, isoxazolyl or thiazolyl each of which is unsubstituted or mono- or di-substituted by lower alkyl;

R is hydrogen; lower alkyl, phenyl-lower alkyl; phenyl which is unsubstituted or mono-, di- or tri-substituted by lower alkoxy, hydroxy, halogen, lower alkyl, trifluoromethyl, or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy or oxy-C₂-C₃-alkylene; a heterocyclic aryl radical selected from pyridyl, thiazolyl and quinolinyl, each unsubstituted or mono- or disubstituted by lower alkyl; biphenyl; biphenyl-lower alkyl; (pyridyl or thienyl)-lower alkyl; trifluoromethyl; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-lower alkyl; (oxa or thia)-C₃-C₆-cycloalkyl, [(oxa or thia)-C₃-C₆-cycloalkyl]-lower alkyl; hydroxy-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl or (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl;

R₁ is hydrogen; lower alkyl; phenyl-lower alkyl wherein phenyl is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl or, on adjacent carbon atoms, by C₁-C₂-alkylenedioxy; biphenyl-lower alkyl; heterocyclic aryl-lower alkyl wherein heterocyclic aryl is selected from thiazolyl, pyrazolyl, pyridyl, imidazolyl and tetrazolyl each unsubstituted or substituted by lower alkyl; C₃-C₁₀-cycloalkyl; C₃-C₇-cycloalkyl-lower alkyl; hydroxy-lower alkyl, (phenyl or pyridyl)-lower alkoxy-lower alkyl; lower alkyl-(thio, sulfinyl or sulfonyl)-lower alkyl; (amino, mono- or di-lower alkylamino)-lower alkyl; (N-lower alkyl-piperazino or N-phenyl-lower alkylpiperazino)-lower alkyl; (morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl or N-lower alkylpiperidyl)-lower alkyl; lower alkanoylamino-lower alkyl; R₃-CONH-lower alkyl wherein R₃ represents (di-lower alkylamino, N-lower alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino or N-alkylpiperidyl)-lower alkyl; piperidyl; pyrrolidinyl; hexahydroazepinyl; N-lower alkyl-

or N-acyl-(hexahydroazepinyl, piperidyl or pyrrolidinyl); C₅-C₁₀-oxacycloalkyl; C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-cycloalkyl; (hydroxy- or oxo-) C₅-C₁₀-thiacycloalkyl; (hydroxy- or oxo-) oxacycloalkyl; (amino, mono- or dialkylamino or lower alkanoylamino)-C₅-C₁₀-cycloalkyl;

R₂ is hydrogen or lower alkyl;

(b) or wherein R and R₁ together with the chain to which they are attached form a thiazolidine or pyrrolidine ring, each unsubstituted or mono- or di-substituted by lower alkyl; and Ar and R₂ have meaning as defined under (a);

(c) or wherein R₁ and R₂ together with the carbon atom to which they are attached form a ring system selected from C₃-C₇-cycloalkane which is unsubstituted or substituted by lower alkyl; oxa-cyclohexane; thia-cyclohexane; and piperidine which is unsubstituted or substituted on nitrogen by lower alkanoyl, di-lower alkylamino-lower alkanoyl, lower alkoxycarbonyl, (morpholino, thiomorpholino or piperidino)-carbonyl, lower alkyl, (phenyl or pyridyl)-lower alkyl, (carboxy, lower alkoxycarbonyl, aminocarbonyl or mono- or di-lower alkylaminocarbonyl)-lower alkyl or by lower alkylsulfonyl; and Ar and R have meaning as defined under (a);

a pharmaceutically acceptable prodrug derivative thereof; or a pharmaceutically acceptable salt thereof.

20. Use according to claim 17, where the compound used is N-hydroxy-2(R)-[[4-methoxybenzenesulfonyl](3-picoly)amino]-3-methylbutanamide or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/IB 95/00464

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/42 C07D223/10 C07D211/34 A61K31/44 A61K31/18
C07D405/12 C07D401/12 C07C311/29 C07D307/16 C07D313/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP-A-0 606 046 (CIBA GEIGY AG) 13 July 1994 cited in the application see the whole document ----	1-20
A	TRENDS IN BIOTECHNOLOGY, vol. 10, no. 6, 1992 CAMBRIDGE GB, pages 200-207, A.J.P. DOCHERTY ET AL 'The matrix metalloproteinases and their natural inhibitors: prospects for treating degenerative tissue diseases.' -----	1-20
A	WO-A-90 05719 (BRITISH BIO TECHNOLOGY) 31 May 1990 see the whole document -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

7 September 1995

Date of mailing of the international search report

18.09.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 95/00464

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK : ALTHOUGH CLAIMS 17-20 ARE DIRECTED TO A METHOD OF TREATMENT OF (DIAGNOSTIC METHOD PRACTISED ON) THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/IB 95/00464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0606046	13-07-94	AU-B- 5265593	04-05-95
		CA-A- 2112779	07-07-94
		FI-A- 940012	07-07-94
		JP-A- 6256293	13-09-94
		NO-A- 940038	07-07-94
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		AU-A- 4800390	12-06-90
		DE-D- 68914687	19-05-94
		DE-T- 68914687	08-09-94
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		ES-T- 2055409	16-08-94
		JP-T- 4502008	09-04-92
		NO-B- 177701	31-07-95
		US-A- 5310763	10-05-94
		US-A- 5240958	31-08-93